**CONCEPT REVIEW**

**Contract Title:** **Multiple-Mouse Strain Studies of Genetic Variation and Host Susceptibility to Toxicity**

**Project Officer:** **Dr. John E. French (919) 541-2569**

**Objectives:** The purpose of this contract is to provide the capacity to use multiple isogenic mouse strains to study the genetic basis for variation in quantitative measures of chemical toxicity *in vivo*. These multidisciplinary studies will permit the National Toxicology Program (NTP) to use the significant genetic diversity within different laboratory and/or wild-derived (isogenic) mouse strains to model and predict potential population-level ranges of response to toxicant exposure. The goal is to support the identification and to understand the functional characterization of specific genes and their allelic variants that are associated with individual differences in response to toxicant exposure. These data will allow the NTP and its partners to use comparative genetic analysis of susceptibility genes discovered in individual strains of mice to identify risks specific to susceptible human populations harboring genetic variations in orthologous genes and pathways, many of which have been cataloged in the NIEHS Environmental Genome Project.

**Background and Concept Statement:** The NTP is launching a new initiative to study the genetic basis for population-level differences in both toxicant and/or disease susceptibility that will lead to a better understanding of how and why substances in our environment are hazardous to some individuals and not to others. Asthma, cardiovascular disease, cancer, diabetes, and obesity are a few examples of diseases associated with multiple interacting genes that are induced or influenced by environmental exposure to toxicants. The Host Susceptibility Initiative (HSI) will provide the NTP with a mechanism for planning, conducting, and analyzing a multi-strain assessment of the chemicals that are associated with human diseases or disease processes (e.g., DNA damage, hormonal signaling, mitochondrial energetics, xenobiotic metabolism, etc.) resulting from gene-environment interactions. The NTP's current research and testing program evaluates and characterizes potential hazards of substances in a limited number of isogenic strains of rats and/or mice following acute to long term exposure. These proposed studies will be conducted consistent with good laboratory practices, but are not intended to be GLP compliant. These studies will require laboratories with scientists who are expert in multiple quantitative measures of chemical toxicity and who have the capacity and expertise to conduct experiments using multiple strains of mice. Thus, a new contract and statement of work (SOW) is required for the conduct of the HSI studies.

Through the HSI, NTP scientists will be able to study chemicals identified as toxicants in the research and testing program and evaluate their effects in multiple, genetically diverse isogenic mouse strains, modeling populations of heterogeneous humans. Results from this initiative will support the determination of which strains and allelic variants are particularly sensitive or insensitive to the chemical exposures causing a specific toxicity and associated disease. These proposed activities are based on the significant genetic variation, haplotype structure, and disease susceptibility that have already been demonstrated in isogenic mouse and rat strains with human predictability[1-5].

In addition, this contract will permit the NTP, through the HSI, to gain added value by performing multi-strain toxicity and phenotyping studies, and provide data and biological samples for further investigation of haplotype-phenotype association through partnerships with the extramural and/or NIEHS/NTP intramural research communities of scientists. Ultimately, the NTP expects to learn more concerning the critical genes and their allelic variants that modulate pathways involved in toxic responses and the etiology of environmental-mediated disease. Such an understanding of gene and environment interactions will lead to more informed research and testing paradigms for both prevention and clinical intervention. Consequently, the HSI will be an integral component of the NIEHS Genes and Environment Initiative.

**References:**


1. Festing, M. F. The case for isogenic strains in toxicological screening. Arch Toxicol Suppl 9, 127-37 (1986).
2. Flint, J., Valdar, W., Shifman, S. & Mott, R. Strategies for mapping and cloning quantitative trait genes in rodents. Nat Rev Genet 6, 271-86 (2005).
3. Guryev, V. et al. Haplotype block structure is conserved across mammals. PLoS Genet 2, e121 (2006).
4. Liu, P. et al. Candidate lung tumor susceptibility genes identified through whole-genome association analyses in inbred mice. Nat Genet 38, 888-95 (2006).
5. Wang, X., Ishimori, N., Korstanje, R., Rollins, J. & Paigen, B. Identifying novel genes for atherosclerosis through mouse-human comparative genetics. Am J Hum Genet 77, 1-15 (2005).